Glycogen synthase kinase 3beta missplicing contributes to leukemia stem cell generation.

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Public Summary:

Scientific Abstract:
Recent evidence suggests that a rare population of self-renewing cancer stem cells (CSC) is responsible for cancer progression and therapeutic resistance. Chronic myeloid leukemia (CML) represents an important paradigm for understanding the genetic and epigenetic events involved in CSC production. CML progresses from a chronic phase (CP) in hematopoietic stem cells (HSC) that harbor the BCR-ABL translocation, to blast crisis (BC), characterized by aberrant activation of beta-catenin within granulocyte-macrophage progenitors (GMP). A major barrier to predicting and inhibiting blast crisis transformation has been the identification of mechanisms driving beta-catenin activation. Here we show that BC CML myeloid progenitors, in particular GMP, serially transplant leukemia in immunocompromised mice and thus are enriched for leukemia stem cells (LSC). Notably, cDNA sequencing of Wnt/beta-catenin pathway regulatory genes, including adenomatous polyposis coli, GSK3beta, axin 1, beta-catenin, lymphoid enhancer factor-1, cyclin D1, and c-myc, revealed a novel in-frame splice deletion of the GSK3beta kinase domain in the GMP of BC samples that was not detectable by sequencing in blasts or normal progenitors. Moreover, BC CML progenitors with misspliced GSK3beta have enhanced beta-catenin expression as well as serial engraftment potential while reintroduction of full-length GSK3beta reduces both in vitro replating and leukemic engraftment. We propose that CP CML is initiated by BCR-ABL expression in an HSC clone but that progression to BC may include missplicing of GSK3beta in GMP LSC, enabling unphosphorylated beta-catenin to participate in LSC self-renewal. Missplicing of GSK3beta represents a unique mechanism for the emergence of BC CML LSC and might provide a novel diagnostic and therapeutic target.

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